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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/653,114	05/24/1996	ERIK S FALCK-PEDERSEN	19603/233(CR)	5761

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EXAMINER

SCHNIZER, RICHARD A

ART UNIT PAPER NUMBER

1635

DATE MAILED: 03/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	08/653,114	FALCK-PEDERSEN, ERIK S
	Examiner	Art Unit
	Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on ____.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1,3,4,9 and 17-20 is/are pending in the application.

4a) Of the above claim(s) ____ is/are withdrawn from consideration.

5) Claim(s) ____ is/are allowed.

6) Claim(s) 1,3,4,9 and 17-20 is/are rejected.

7) Claim(s) ____ is/are objected to.

8) Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on ____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on ____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. ____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.

4) Interview Summary (PTO-413) Paper No(s) ____.
5) Notice of Informal Patent Application (PTO-152)
6) Other: _____

DETAILED ACTION

An amendment was received and entered as Paper No. 41 on 1/9/02. Claims 1, 3, 4, 9, and 17-20 remain pending and are under consideration in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 4, 9, and 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3, 4, 9, and 17-20 are indefinite because they recite "the direction of adenoviral gene transcription" without antecedent basis. It is well known in the art that adenoviral gene transcription proceeds in both directions. See e.g. Horwitz (In *Fundamental Virology*, Second Edition, B Fields, D. Knipe et al Eds. Raven Press, Ltd. New York, 1991), Fig. 5, at page 780, which shows that E1 and E3 mRNAs are transcribed in the opposite direction to E2 mRNAs. Thus one of skill in the art cannot know in which orientation Applicant intends the expression cassette to be inserted into the vector.

These claims are also indefinite because they require that the vector must comprise an insertion site which is oriented opposite to the direction of gene transcription, however the art does not teach that orientation sites have any particular orientation, and the specification fails to teach how to determine the orientation of an insertion site. For example, most insertion sites are restriction sites, many of which are

palindromic and can have no orientation. Regarding those restriction sites which are not palindromic, neither the specification nor the prior art of record provide any standard for arbitrarily determining what is the orientation of a particular non-palindromic restriction site.

Claim Rejections - 35 USC § 103

Claims 1, 3, 4, 9, and 17-20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Kirshenbaum *et al.*, Quantin *et al.*, or Stratford-Perricaudet *et al.*; in view of Huang *et al.*, Choi *et al.*, Keating *et al.*, and KabiGen, for the reasons of record in Paper no. 40.

The invention is an adenoviral expression vector comprising at least one gene insertion site, a heterologous promoter upstream of the insertion site, eukaryotic splice acceptor and donor signals positioned downstream of the promoter and upstream of the insertion site, and a polyadenylation signal downstream of the insertion site. The promoter may be the mouse CMV early promoter. The polyadenylation signal may be the mouse beta-globin polyadenylation signal. A form of the vector containing a heterologous sequence inserted into the insertion site is claimed, as is a unicellular host transformed with the vector. Methods of producing a selected protein by culturing infected or transformed hosts with the claimed vectors are also claimed.

Kirshenbaum *et al.* disclose a plasmid vector having Ad5 sequences which, when cotransfected with a mutant Ad5 construct into 293 cells, can recombine to produce a replication-incompetent virus containing the plasmid expression cassette (entire document, e.g. Methods). The replication cassette contains the human CMV promoter, the lacZ gene and the SV40 polyadenylation signal sequence. Within the plasmid, the

expression cassette is flanked by Ad5 sequences that read on the left end packaging and replication sequences and homologous recombination sequences recited in claim 1. Kirshenbaum *et al.* also disclose transfected host cells producing b-galactosidase. Quantin *et al.* and Stratford-Perricaudet *et al.* each disclose similar products and methods, only different promoter and polyadenylation sequences are used in the expression cassette. None of the above three references discloses an expression cassette containing a splice site between the promoter and the gene to be expressed, nor do they disclose the use of the murine CMV early promoter and murine b-globin polyadenylation signal sequences. Huang *et al.* teach that including a splice site in the 5' untranslated portion of the gene to be expressed resulted in a much higher level of gene expression in several cell lines, including 293 (entire document, e.g. Fig. 2). Furthermore, Choi *et al.* (abstract) teach that incorporation of a generic intron between the promoter and the gene of interest causes 5- to 300-fold increases in transgene expression in mice. Keating *et al.* teach that the murine immediate early CMV promoter produces a high level of gene expression in transfected cells (Table 1, Fig. 1). The KabiGen disclosure teaches that polyadenylation sequences from rodent b-globin genes yield efficient RNA processing in transfected cells (p5, lines 10-15). KabiGen also discloses vectors which contain additional cloning sites for insertion of additional genes (Figures).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the expression cassette of Kirshenbaum *et al.*, Quantin *et al.*, or Stratford-Perricaudet *et al.*, by including the splice site of either Huang *et al.* or Choi *et al.*, the murine CMV promoter of Keating *et al.*, and the murine b-globin polyadenylation sequence suggested by KabiGen. One skilled in the art would have been motivated to use these components in the expression cassette, given their

recognized value for promoting high level gene expression and given the expectation that each component would continue to function in its known and expected manner. Thus the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

With respect to claim 20, it is noted that Stratford-Perricaudet teaches a method delivering heterologous genes to an animal heart *in vivo*. It would have been obvious to one of ordinary skill in the art to use in the method of Stratford-Perricaudet the vector obtained through the combination of the references cited above. One would have been motivated to do given the reasonable expectation that the vector would give enhanced gene expression.

Thus the invention as a whole was *prima facie* obvious.

Response to Arguments

Applicant's arguments of record have been fully considered as they pertain to the preceding rejection, but they are not persuasive.

Applicant argues that the cited references fails to teach a vector comprising an expression cassette oriented in the direction opposite to adenoviral gene transcription. This is unpersuasive because it is well known in the art that adenoviral genes are located on both strands of the virus. See e.g. Horwitz (In *Fundamental Virology*, Second Edition, B Fields, D. Knipe et al Eds. Raven Press, Ltd. New York, 1991), Fig. 5, at page 780, which shows that E1 and E3 mRNAs are transcribed in the opposite direction to E2 mRNAs. For this reason, adenoviral gene transcription must proceed in each direction, thus all adenoviral expression vectors comprise expression cassettes which are oriented both opposite to, and with, the direction of adenoviral gene transcription.

For this reason the rejection is maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Katrina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.



JAMES KETTER
PRIMARY EXAMINER